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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF
LIFEN SHEN, ET AL
APPLICATION NO: 10/788,825
FILED: 02/27/2004
FOR: A NON-CRYOGENIC PROCESS FOR FORMING GLYCOSIDES

ART UNIT: 1623
EXAMINER: KRISHNAN, GANAPATHY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR 1.132

Sir:

This declaration by Lifen Shen, Ph.D. is submitted concurrently with a Supplemental Amendment in response to the Final Office Action dated October 12, 2005.

DECLARATION OF DR. LIFEN SHEN

Lifen Shen declares that

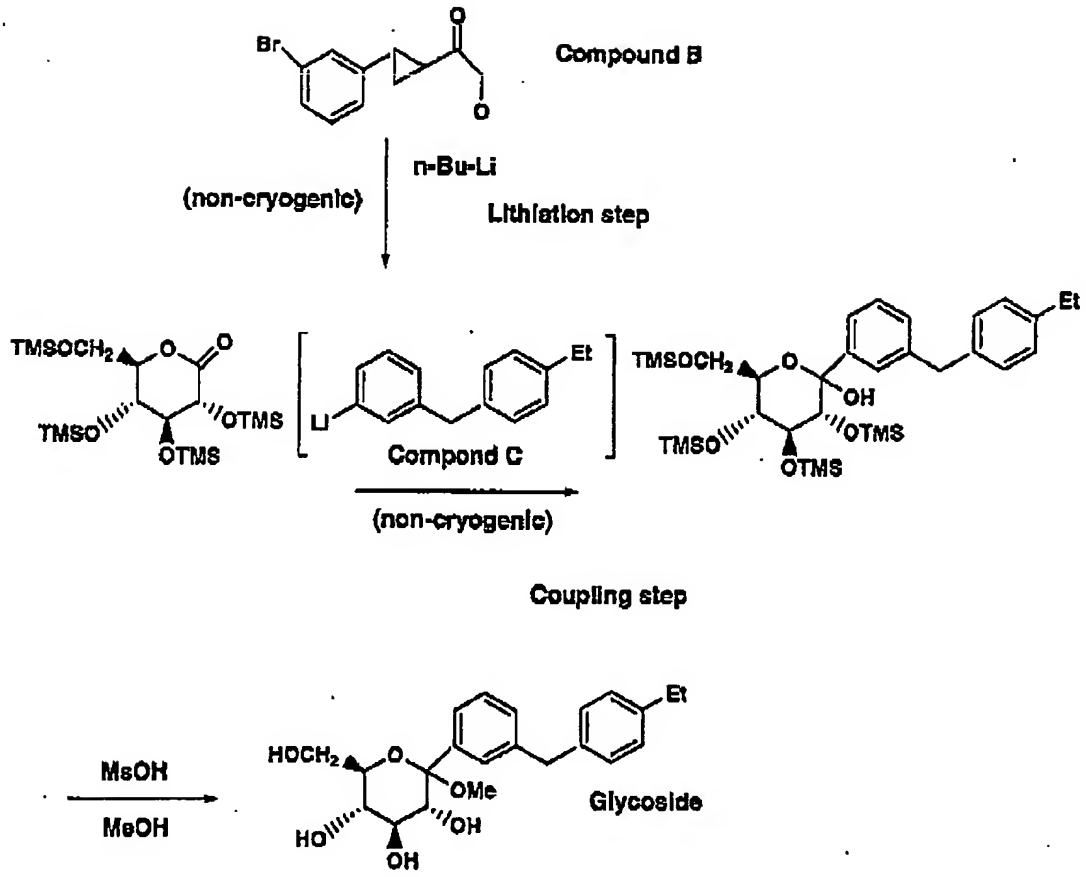
1. She holds a Ph.D. in Chemical Engineering awarded by the Massachusetts Institute of Technology, and presently is employed as a Senior Research Investigator by the assignee of record, Bristol-Myers Squibb Company.

2. She is a named inventor in the U.S. Patent Application No. 10/788,825.

3. During the development of the glycoside formation process claimed in this application, she conducted several experiments to determine the effect of performing the glycoside formation process using a microreactor, for at least one phase of the technique, at a non-cryogenic temperature, which is a temperature above -20°C. She also conducted comparative experiments on glycoside formation at non-cryogenic temperatures without use of a microreactor, i.e., by a conventional batch process, and using the conventional batch process at cryogenic temperature.

4. The process referred to herein as a batch process is comparable to that described in a journal reference recently cited by the Examiner, Czernecki et al., J. Org. Chem. 1991, 56, 6289-6292 (hereinafter referred to as "Czernecki"), wherein a lithiation step and coupling step were performed under small scale batch conditions (total reaction volume <20 ml; Czernecki at 6291). In one example of Czernecki, arylithium compounds 3a were first prepared by adding sec-butyllithium dropwise to aryl bromide in 3 ml of solvent at room temperature, then transferred to a solution of the gluconolactone (compound 1) that had been cooled to -78°C (see page 6291, column 1, paragraph 9 to column 2, second paragraph, General Procedure for the Preparation of Aryllithium Derivatives 3a and 3b) for the coupling reaction (see page 6290, column 2, second full paragraph, and Scheme II, first step). The product of the coupling step, a compound dissimilar from the glycosides of the present invention by virtue of the scope of the molecular substitution, was produced in a yield of only 62%, even though the lithiation step was performed at room temperature.

5. The process of the invention and the comparative experiments were carried out to prepare a glycoside compound according to the scheme presented below.



The above scheme may be correlated with the general scheme for the conventional batch process at page 2 of the Specification (Scheme A), and also with the general scheme for processes according to the invention at page 21 (Scheme D). A single scheme is presented here because the reaction chemistry is the same; the scheme, however, remains generic to both the conventional batch process and the continuous microreactor process of the invention with respect to the temperature conditions that are relevant to the operation of the presently claimed invention. For each preparation, a lithiated compound, C, was formed, in a first step, by a stoichiometric reaction with n-butyl-lithium in an organic solvent system at selected temperature conditions, reported in Table A, set out below, to achieve lithiation and coupling. The selected temperature according to the level of knowledge in the prior art at the time of this invention was to conduct this lithiation step at cryogenic temperatures, followed by coupling at cryogenic temperatures, as shown in Applicants' Specification at Scheme A (page 2). Such a process is represented by Control 3 of Table A below. Experiments

according to the invention were conducted by performing the lithiation at non-cryogenic temperatures, i.e. temperatures above -20°C, in a continuous microreactor (see Examples 4-6) and in a batch process (See Controls 1 and 2).

6. As shown in Table A, the selected solvent system for each particular step in these comparative examples were selected from THF/heptane or THF/toluene.

7. The lithiation was followed by a coupling step. Referring to the data presented in Table A below, for Controls 1 and 2, and Examples 4-6 according to the invention, this step was conducted at non-cryogenic temperatures, i.e. above -20°C.

8. A further deprotection step was accomplished *in situ* for the continuous microreactor process, while for the controls performed according to the batch process, deprotection was accomplished in either heptane or hexane.

9. For each experiment, the isolated yield of glycoside was determined. Results are reported in Table A.

Table A: Preparation of Glycoside

Process	Ex.	Scale (g)	Conditions		Isolated Yield
			Lithiation (solvent, temperature)	Coupling (solvent, temperature)	
Batch processes as run in the standard lab glassware	Control 1	3.0	THF/heptane, -10°C	THF/heptane, -10°C	40.3%
	Control 2	3.0	THF/heptane, 20°C	THF/heptane, 20°C	32.2%
	Control 3	3.0	THF/heptane, -78°C	THF/heptane, -78°C	83.6%
Continuous processes run using a microreactor system (two non-cryogenic steps)	Ex. 4	4.0	THF/heptane, 20°C	THF/heptane, -10°C	76.3%
	Ex. 5	4.0	THF/heptane, 20°C	THF/heptane, 5°C	72.1%
	Ex. 6	4.0	THF/heptane, 20°C	THF/heptane, 20°C	70.4%

10. The data shows that the conventional batch process, typified by the Controls 1 and 2, when modified for the purpose of comparison to the present invention to be performed (both steps) at non-cryogenic temperatures, produced yields of isolated product of 40.3% and 32.2%, respectively. When the batch process was performed as it is conventionally known, under cryogenic temperature conditions (-78°C), the isolated yield was elected to 83.6% (Control 3).

11. In comparison, the Examples 4 to 6 representative of embodiments of the invention demonstrated that performing the lithiation step alone, or the lithiation and coupling steps together in a continuous microreactor under non-cryogenic temperature conditions produced better yields than obtained by the batch process at comparable temperatures (Controls 1 and 2). For Examples 4-6, the lithiation was conducted at a non-cryogenic temperature of 20°C in each case, while the coupling step was also conducted at a non-cryogenic temperature (-10, 5 and 20°C, respectively). For Examples 4 to 6, the corresponding isolated yields ranged from 70.4% to 76.3%. These yields were significantly higher than reported for the batch process performed at non-cryogenic temperatures (Controls 1 and 2, 40.3% and 32.2%, respectively).

12. She hereby declares that all statements made herein of her own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful statement may jeopardize the validity of the application of any patent issued thereon.

Aug 31, 2006.
Date:

Lifen Shen, Ph.D.

Aug 31, 2006
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